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UNITED STATES DISTRICT COURT

FOR THE SOUTHERN DISTRICT OF CALIFORNIA

BECKMAN COULTER INC. and ORCHID CELLMARK INC.,

Plaintiffs,

v.

SEQUENOM, INC.,

Defendant.

AND RELATED COUNTERCLAIM

Case No. 08 CV 1013 MMA POR

DECLARATION OF DR. LARRY J. KRICKA IN SUPPORT OF BECKMAN COULTER INC. AND ORCHID CELLMARK INC.'S RESPONSIVE CLAIM CONSTRUCTION BRIEF

Date: June 11, 2009
Time: 1:30 p.m.
Location: Courtroom 5
Judge: Honorable Michael M. Anello

I, Dr. Larry J. Kricka, declare as follows:

1. I have been retained as an expert by Plaintiffs Beckman Coulter Inc. and Orchid Cellmark Inc. ("Plaintiffs"). This Declaration is submitted in support of Plaintiffs' Responsive Claim Construction Brief ("Pl. Resp. Br."). I have personal knowledge of the matters stated herein and if called to testify as a witness, I could and would competently testify thereto.

2. I incorporate by reference my Declaration In Support of Plaintiffs' Opening Claim Construction Brief ("Kricka Decl.") including, but not limited to, my professional background and the opinions contained therein.

I. TASK

3. I was asked review the following U.S. Patents: U.S. Patent Nos. 5,888,819 (the " '819 patent"), 6,004,744 (the " '744 patent"), and 6,537,748 B1 (the " '748 patent") (collectively, the "patents-in-suit"). I was asked to provide expert opinion testimony that would assist the Court in determining the meaning of claim terms of the patents-in-suit.

II. MATERIALS CONSIDERED

4. My opinions are based on my educational background, industry knowledge, research in the relevant technology of the patents-in-suit, and understanding of basic science principles and practices. As part of my analysis of the patents-in-suit and forming the basis of the opinions in this report I have considered the patents-in-suit, their prosecution histories, the references cited in the patents-in-suit, and the proceedings of the two interferences. At times, I also reviewed extrinsic evidence cited by the parties, including relevant section of dictionaries and scientific journal to confirm the ordinary meaning of some of the terms.

5. I also reviewed the Joint Claim Construction Charts, Joint Claim Worksheets And Joint Hearing Statement ("the Joint Statement") that were filed on February 20, 2009. In Exhibit B of the Joint Statement, both parties present their proposed definitions for the claim terms, as well as the intrinsic and extrinsic evidence that the parties rely on in support of their respective definition. Additionally, I reviewed Sequenom's Opening Claim Construction Brief ("Def. Br."), Dr. Sutherland's Declaration in support of Sequenom's Opening Claim Construction Brief ("Sutherland Decl."), and the evidence cited by Sequenom in support of Defendant's brief. I also reviewed the deposition transcript

of Dr. Sutherland ("Sutherland Dep.") I used these documents to consider and analyze the proposed claim constructions of the parties.

III. DISPUTED CLAIM TERMS

6. In this section, I analyze and respond to Defendant's construction of the disputed terms of the patents-in-suit. It should be noted that simply because I do not address every point made by Defendant or Dr. Sutherland, Defendant's expert, it does not mean that I agree with Defendant or Dr. Sutherland. Moreover, I may supplement this declaration if I become aware of additional pertinent information or in response to the testimony of others, including witnesses who testify or submit reports or declarations on behalf of Defendant.

A. "In The Absence Of dATP, dCTP, dGTP, or dTTP," "In The Absence Of Non-Terminator Nucleotides," And "Lacks dATP, dCTP, dGTP And dTTP"

7. I understand that both parties agree that "absence" and "lacks" should have the same meaning. For simplicity, I will use the term "absence" to refer to both "absence" and "lacks." Defendant's proposed construction requires that there is absolute purity of certain mixtures used with the claimed inventions. I disagree with Defendant's proposed construction. I also disagree with Dr. Sutherland's opinion about "absence" and "lacks".

8. In response to Plaintiffs' demonstration that Example 2 in the patents-in-suit shows that washing is not perfect and therefore one of ordinary skill in art would recognize a trivial amount of contaminants would be present in the claimed inventions, Dr. Sutherland has argued that that Example 2 only shows unincorporated terminator nucleotides and not non-terminator nucleotides in the background as contaminants. (*See* Sutherland Decl., ¶30). Therefore, he argues, Example 2 does not demonstrate or suggest the presence of a "trivial" amount of unlabeled non-terminator nucleotides. However, I disagree with Dr. Sutherland's contention that Example 2 does not support Plaintiff's proposed construction.

9. Example 2 discloses the efficiency of a washing procedure using beads. The patents-in-suit disclose that the "background in this experiment due to non-specific label from all other sources was approximately 3-4%." ('819 patent, at 18:25-27). I agree with Dr. Sutherland that for Reaction B, the background is predominantly ddNTPs. However, one of ordinary skill in the art would recognize the applicability of this calculation to dNTPs. The only difference between ddNTPs and dNTPs is that a

ddNTP has one fewer hydroxyl group than a dNTP. Therefore, Dr. Sutherland's argument does not make sense. The background due to ddNTPs sticking to the beads still provides an indication of the background that would be encountered using dNTPs.

10. Notwithstanding Dr. Sutherland's contention that the calculation only applies to ddNTPs, the table in Example 2 discloses enough information to calculate the percentage of background related to dNTPs. The percentage calculated in Example 2 ('819 patent, at 18:25-27) was only for Reaction B. Reaction A (ignored by Dr. Sutherland) provides data on the background that was observed using dNTPs. It is possible to calculate the background from the raw data provided for Reaction A which consists of dNTPs. The highest background signal from the controls in the "A" reaction for Template 180 is 5187 cpm of ^{35}S for a reaction with no polymerase and this represents ~1.6% when compared to the positive control (A, complete; 325,782 cpm of ^{35}S). In the "A" reaction for Template 181 the highest background signal from the controls is 12,386 cpm of ^{35}S (A, no primer) and this represents ~2.8% when compared to the positive control (A, complete; 441,823 cpm of ^{35}S). The latter value of ~2.8% is very close to the approximately 3-4% value cited for the ddNTPs and indicates that that background due to failure of the washing step to remove nucleotides from the magnetic beads is similar for ddNTPs and dNTPs. Thus, one of ordinary skill in the art would understand that the reaction mixture, after the washing procedure step would contain a trivial amount of dNTPs. Defendant's argument that Example 2 is not applicable to the claim construction of "absence" is without merit.

11. During Dr. Sutherland's deposition, he argued that the "General Methods" section of the specifications describe techniques which would remove all dNTPs, and that such techniques must be incorporated into the preferred embodiment. (Sutherland Dep., at 122:9-123:20). I disagree with this contention because one of ordinary skill in the art would have no reason to practice these methods in addition to what is disclosed in the preferred embodiment.

12. The General Methods section discloses a procedure called phenol/chloroform extraction and ethanol precipitation. ('819 patent, at 16:59-63). This method was well-known by one of ordinary skill in the art as a method of purifying DNA. However, one of ordinary skill in the art would understand that such a purification step would be unnecessary to practice the preferred embodiment.

13. One of ordinary skill in the art would understand that the preferred embodiment teaches a

simplified and specific method for cleaning the DNA. In fact, the specification states that the preferred embodiment is "a particularly advantageous way to practice the present invention." ('819 patent, at 21:27-28). Direct capture of biotinylated PCR products was a known procedure and would been familiar to one of ordinary skill in the art. (*See e.g.*, '819 patent, at 16:63-66). Moreover, the procedure disclosed in the preferred embodiment is amenable to automation as opposed to a phenol/chloroform extraction and ethanol precipitation. Phenol/chloroform extraction and ethanol precipitation is a time consuming and unnecessary step. The preferred embodiment discloses that its preferred procedure is in line with automating the methods of the claimed invention. ('819 patent, at 22:56-65). One of ordinary skill in the art would understand that if a goal to automate the process of single base extension, then it would be extremely difficult to automate a phenol/chloroform extraction and ethanol precipitation step. In short, it would make no scientific sense at all to use the purification step from the "General Methods" section in connection with the preferred embodiment. Thus, I disagree with Dr. Sutherland's contention that one would import these methods of cleaning into the preferred embodiment.

B. "Terminator" And "Nucleotide Terminators, Or Terminator Nucleotide Analogs"

14. I disagree with Defendant's proposed construction of "terminator," which I understand is a "molecule, including a nucleotide, nucleotide analog, dideoxynucleotide, or arabinoside triphosphate, that when incorporated onto the 3' end of a primer is capable of specifically terminating the extension reaction and inhibiting further elongation." A person of ordinary skill in the art would understand that the term "terminator" means "a nucleotide or nucleotide analog, which after being incorporated onto the 3' end of a primer, does not permit any further extension of the primer."

15. Defendant's proposed construction of "terminator" permits it to be "capable of specifically terminating the extension reaction and inhibiting further elongation." (Def. Br., at 18-19). Under this construction a "terminator" can allow more than one nucleotide to be added to the primer because a terminator needs to only "inhibit" and not to actually terminate the reaction. I disagree with this construction because it would not allow for identification of the single nucleotide of interest which is the purpose of the claimed inventions of the patents-in-suit.

16. One of ordinary skill in the art would understand that in order to achieve the goals of the claimed invention a "terminator" must not permit any further extension of the primer. Indeed, Dr.

Sutherland admitted in his deposition that the patents-in-suit describe no embodiments where primer extension occurs after the incorporation of the terminator. (Sutherland Dep., at 102:19-23). One of ordinary skill in the art would understand that a "terminator" must, once incorporated onto the primer, stop extension and terminate the reaction.

17. Defendant contends that claim 1(c) of the '819 patent supports its construction. (Def. Br., at 19). I disagree with Defendant. Defendant points to "capable of specifically terminating the extension reaction" in claim 1(c) as further support for its contention that a terminator need to only inhibit elongation instead of actually terminate the reaction. However, one of ordinary skill in the art would look at the entire claim language to inform its construction. One of ordinary skill in the art would understand that in order to practice the claimed invention the primer could only be extended by one terminator. Thus, the terminator must actually terminate the reaction. Adopting Defendant's construction would ignore the context of the claim resulting in an outcome that frustrates the fundamental purpose of the inventions.

18. Defendant's construction lists nucleotides, nucleotide analogs, dideoxynucleotides and arabinoside triphosphates as terminators. (Def. Br., at 18). However, dideoxynucleotides and arabinoside triphosphates are a type of nucleotide analogs. One of ordinary skill in the art would understand a nucleotide analog is simply any structure that is related to a nucleotide but whose chemical and biological properties may be different. Thus, there is no reason to specifically separate out dideoxynucleotides and arabinoside triphosphates as terminators when they are encompassed in the group called "nucleotide analogs."

19. Defendant argues that terminators need only inhibit further elongation rather than terminate further extension. (Def. Br., at 19, citing Sutherland Decl., at ¶ 59). Defendant cites arabinoside triphosphates as an example of a nucleotide analog that inhibits instead of terminates. I disagree with Defendant's proposed construction because one of ordinary skill in the art would understand that arabinoside triphosphates are terminators as the phrase is used by Plaintiffs.

20. One of ordinary skill in the art would know how to use an arabinoside triphosphate to terminate extension and achieve the objective of the invention. Arabinoside triphosphates have long been recognized as terminators. The seminal paper on dideoxy sequencing disclosed the use of

arabinoside triphosphates as terminators. (Sanger et al., "DNA sequencing with chain-terminating inhibitors," Proc. Nat'l Acad. Sci. 74(12): 5463-5467 (1977)). Dr. Sutherland agrees: "arabinose as Sanger demonstrated, could be used profitably in chain termination DNA sequencing." (Sutherland Dep., at 51:9-11; *see also*, Sutherland Dep., at 53:8-18, 103:22-104:2). The Sanger paper acknowledged that arabinoside triphosphates can further extend the reaction. However, the paper limits this inhibitory action to the presence of only "some mammalian DNA polymerases." *Id.* at 5463. This means one of ordinary skill in the art would understand that under appropriate conditions arabinoside triphosphates can be used effectively to actually terminate the extension as opposed to simply inhibit elongation.

21. Even if conditions are used that would allow for the arabinoside triphosphate to inhibit elongation rather than terminate extension, the ability of arabinoside triphosphate to extend is significantly slower than a dideoxynucleotide. The paper cited by Dr. Sutherland in his declaration states that the ability of arabinoside triphosphates to extend beyond the single base is thousands of times slower than normal rates of extension even at optimal conditions. (Perrino et al., "Incorporation of Cytosine Arabinoside Monophosphate into DNA at Internucleotide Linkages by Human DNA Polymerase α" J. Biol. Chem. 267(32): 23043-51 (1992))). Other papers support this finding. (Mikita and Beardsley, "Functional Consequences of the Arabinosylcytosine Structural Lesion in DNA." Biochemistry 27: 4968-4705 (1988)). Thus, even if arabinoside triphosphates are capable of inhibiting, they are very weak inhibitors. One of ordinary skill in the art would understand that the function of a "terminator" as used in the patents-in-suit is to actually terminate extension rather than inhibit elongation. Thus, I agree with Plaintiffs' proposed construction and disagree with Defendant's proposed construction.

22. Defendant contends I support its argument that any kind of terminator can be used, regardless of whether it inhibits rather than terminates. (Def. Br., at 19, citing Kricka Dep., at 142:15-144:18). However, this completely mischaracterizes my testimony. As I explained in my declaration and repeatedly in my deposition, "any sort of terminator can be used as long as it achieves what's in the patent claim, which is incorporation of just the terminator". (Kricka Dep., at 144:15-18, *see also*, Kricka Dep., at 144:23-145:2 ("I'm not sure what are the types of terminators you have in mind here, but as long as the terminator terminates the reaction after a single base extension, then that would seem

to fit within the bounds of the patent")).

C. "Detectable Marker" And "Detectable Label"

23. There are several claim terms and phrases relating to "detectable marker" and "detectable label." They include "wherein at least one of said terminators is labeled with a detectable marker," "at least one of the terminators being labeled with a detectable marker," "labeled with a detectable marker," and "labeled terminators." I understand that the parties have agreed that detectable marker and detectable label have the same meaning. I disagree with Defendant's proposed construction of the terms.

1. A "Detectable Marker" Does Not Need To Be Detected Using A Moiety's "Distinguishable Properties."

24. Defendant claims that it is the moiety's distinguishable property that makes it a detectable marker. I disagree with this contention.

25. As I have previously stated, the specifications list a variety of suitable detection methods. (Kricka Decl., ¶77-82). Contrary to Defendant's contention, the specifications do not limit detection to only a moiety's "distinguishable properties."

26. As an initial matter, detectability and distinguishability are two separate properties of a label. The primary property of a label is the property that makes it detectable. For a fluorescence label, it is detectable because it fluoresces. A secondary property of the label provides distinguishing features, such as its fluorescence spectrum (the color of the fluorescence) or the timescale of the fluorescence emission (rapid or delayed emission of the fluorescence light emission) in the case of a fluorescent label.

27. The difference between detectability and distinguishability is exemplified by claims 1 and 3 and the preferred embodiment of the '819 patent in the context of a fluorescent label. Claim 1 of the '819 patent is an independent claim that covers a method of determining nucleotide of interest. Claim 1 requires that only a single label is employed. ('819 patent, at 30:44-45). Because only one label is used the only requirement is that it is detectable. There is no need to distinguish it from any other labels because only one label is present.

28. In contrast, the method of dependent claim 3 requires that the four labels are not only

detectable but are also distinguishable. ('819 patent, at 30:65-67). Thus, this claim requires that the labels also be differentiated in some aspect. However, there are many claims in the patents-in-suit that require only one "detectable marker," and thus it makes no sense to require those "detectable markers" be distinguishable from any other "detectable marker."

2. A "Detectable Marker" Is Not Required To Be "Attached Or Incorporated In" A Terminator

29. Defendant claims that the detectable marker is something "attached or incorporated" into the terminator and thus is distinct from the terminator. I disagree with Defendant's contention.

30. Defendant has added the "incorporated" language into its proposed construction. (Def. Br., at. 22). However, Defendant's language is unclear as to the scope of what "attached or incorporated" means. Defendant and Dr. Sutherland state that a radioactive moiety can be described as either "attached" or as "incorporated." (Def. Br., at 23). Defendant also cites to examples of fluorophores attached to the terminator. (Def. Br., at 21). However, as I have previously stated there were many nucleic acid labeling techniques known in the art. (Kricka Decl., ¶¶ 77-89). In his deposition Dr. Sutherland confirmed that modification techniques were well-known including covalent attachment, physical binding and incorporation. (Sutherland Dep., at 168:17-25). Thus, Defendant's limitation on detectable marker is inappropriate and should be rejected.

D. "By Detecting The Detectable Marker Of Said Incorporated Terminator"

31. I disagree with Defendant's proposed construction of "by detecting the detectable marker of said incorporated terminator," which I understand is as follows: "by determining the identity of the detectable marker attached to or incorporated in said incorporated terminator using the detectable marker's distinguishable properties."

32. I disagree with Defendant's construction because it includes the requirements that the detectable marker must be "attached to or incorporated in" the terminator, and that the detectable marker must also be identified using the marker's "distinguishable properties." For the reasons set forth in the sections above, as well as in my prior declaration, one of ordinary skill in the art would understand that both of these requirements should not be present in a proper construction of this claim language.

33. I also disagree with Defendant's proposed construction due to the way in which it

interprets the word "detecting." This word is used in an ordinary way in the patents-in-suit. One of ordinary skill in the art would understand it to have its ordinary dictionary definition, which is "discovering the presence or existence of" the item being detected. The American Heritage Dictionary, for example, states that "detect" means "to discover or discern the existence, presence, or fact of." Yet, Defendant's construction does not interpret "detecting" in this manner. Instead, Defendant's proposed construction appears to interpret "detecting" to mean "determining the identity of." This interpretation is not correct. The claim language refers to "detecting" the detectable marker, not "identifying" it. Additionally, the claim language uses the term "detecting" in connection with one nucleic acid (detecting a detectable marker of an extended primer), and it uses the term "identity" in reference to a different nucleic acid (the nucleic acid of interest). ('819 patent at 30:52-55). One of ordinary skill in the art would therefore understand that "detecting" and "identifying" have different meanings in claim 1 of the '819 patent. As a result, they should be not treated as synonyms.

I declare under penalty of perjury of the laws of the United States that the foregoing is true and correct. Executed this 24th day of April, 2009, in Portland, Oregon.

LARRY J. KRICKA. Ph. D.

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CERTIFICATE OF SERVICE

I hereby certify that counsel of record who are deemed to have consented to electronic service are being served on April 24, 2009 with a copy of this document via the Court's CM/ECF system per Local Rules and Administrative Policies Section 2(d).

Any other counsel of record will be served by electronic mail, facsimile transmission and/or first class mail on this same date.

/s/ Matthew R. Hulse
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